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HOMOLOGY MODELING AND MOLECULAR DYNAMICS STUDIES OF THE OLIGOPEPTIDASE B FROM *SERRATIA PROTEAMACULANS*. INSIGHTS INTO THE ENZYMATIC ACTIVATION MECHANISM

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The Oligopeptidase B (OpdB; EC 3.4.21.83) is a trypsin-like peptidase belonging to the family of serine prolyl oligopeptidases (clan SC, family S9), named after the archetypical member of this family, prolyl oligopeptidase (POP) [1]. A characteristic feature of all serine proteases of POP family is an unusual seven-bladed β-propeller N-terminal domain that impedes penetration of large globular protein molecules into the active center located in a cavity at the interface with C-terminal catalytic domain. The known OpdB enzymes from both parasitic protozoa and infection bacteria are important virulence factors of the corresponding infections and can be promising targets for therapeutic treatment upon development of their selective inhibitors by structure-based rational design [2].

Only two protozoan OpdBs' crystal structures have been obtained, namely from *L. major* and *T. brucei*. The 3D structure of *L. major* OpdB demonstrates the importance of the interface between the catalytic and propeller domains for enzymatic activity and stability of the protein [3]. This interface comprises 123 amino acid residues and is stabilized by 29 hydrogen bonds as well as 5 salt bridges between 5 pairs of charged residues, creating a buried surface area. The three-dimensional structure of *T. brucei* OpdB was determined for both an open (inactive) and closed (active) forms of the enzyme and a key role of one from five aforementioned salt bridges in the transition of one form to another was postulated [4]

However, these salt bridges - the important element in the molecular architecture of protozoan OpdBs are not conserved in γ -proteobacterial OpdBs including the peptidase from *Serratia proteamaculans* (PSP), which was the object of our study.

In this work, using comparative modeling and protozoan OpdBs crystal structures [3, 4] we created 3D models of PSP in open and closed forms to elucidate the mechanism underlying PSP activation. The analysis of the models allowed identifying charged amino acid residues surrounding the catalytic triad His652 and participating in the formation of inter-domain contact interface between catalytic and β-propeller domains. Further analysis of the models using molecular dynamic simulation allowed demonstrating the differential stability of the previously founded interdomain contacts and proposing the potential mechanism of the PSP and other γ-proteobacterial OpdBs activation. The results may be useful for either modulation of enzymatic features of bacterial OpdBs or development of their small molecule inhibitors.

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